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NATURAL RESOURCES DEFENSE COUNCIL
CRITIQUE OF THE NAS-NRC REPORT
"HEALTH EFFECTS OF ALPHA-EMITTING
PARTICLES IN THE RESPIRATORY TRACT"*

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Thomas B. Cochran

March, 1977

INTRODUCTION

The purpose of this document is to comment on the NAS Report related to hot particles. Briefly, there are three major flaws in the NAS-NRC Report:

1. The authors failed to discuss the observations related to hot particle produced lesions in human palmar tissue, in rat lungs and in hamster lungs. These hot particle lesions were of highly suspect prognosis -- suspect because the lesions were indicative of an incipient carcinogenic response.

*/ EPA 52014-76-013, a report prepared by the Ad Hoc Committee On "Hot Particles" of the Advisory Committee on the Biological Effects of Ionizing Radiation of the National Academy of Sciences-National Research Council, Washington, D.C., April 1976 (herein-after the NAS Report).

2. The authors misstated our hot particle hypothesis. (This occurred, even though as acknowledged in the Preface of the report, that we had met with the committee to discuss our views.) As a consequence, the ensuing discussion in the report does not address the NRDC hypothesis but addresses this misstated hypothesis. It is, therefore, almost irrelevant and certainly grossly misleading.

3. The authors base a major portion of their conclusion on an erroneous analysis of the cancer induction in beagle dogs following inhalation of plutonium particles.

We shall discuss each of the major flaws in turn and this will be followed by a page-by-page critique of the other material presented in the body of the NAS Report and its Appendices.

HOT PARTICLE PRODUCED LESIONS

Subsequent to the submission of our petition to the EPA to amend plutonium standards as they relate to hot particles, the EPA held public hearings on Plutonium and Other Transuranics. In our Supplemental Submission to those hearings^{*/} we emphasized that hot particles had produced lesions of highly suspect prognosis -- suspect because the lesions were indicative of an incipient carcinogenic response. The following appears on pages 4-7 of our Supplemental Submission:

^{*/} NRDC Supplemental Submission to the Environmental Protection Agency Public Hearings on Plutonium and the Transuranium Elements, February 24, 1975.

"The potential hazard of a single hot particle embedded in human tissue is illustrated by the observation of Lushbaugh and Langham.⁷ They excised a nodule that developed around a Pu-239 particle embedded in the palm of a machinist. Commenting on the histological examination of the lesion, the authors state:

'The autoradiographs showed precise confinement of alpha-tracks to the area of maximum damage and their penetration into the basal areas of the epidermis, where epithelial changes typical of ionizing radiation exposure were present. The cause and effect relationship of these findings, therefore, seemed obvious. Although the lesion was minute, the changes in it were severe. Their similarity to known precancerous epidermal cytologic changes, of course, raised the question of the ultimate fate of such a lesion should it be allowed to exist without surgical intervention⁸'

"Considering the above observations, it would be surprising indeed if a physician would not suggest surgical intervention in a case where a patient had a few such embedded particles. We feel that this lesion alone should cause one to be very cautious in estimating the hazard of hot particles.

^{7/} Lushbaugh, C.C. and J. Langham, "A dermal lesion from implanted plutonium," Archives of Dermatology 86, October 1962, pp. 121-124.

^{8/} Ibid., p. 462.

"That such lesions can develop in lung tissue is supported by the observations of Richmond, et al., on the lesions induced in experiments wherein hot particles were introduced into blood vessels of the lungs of rats:

'Such a lesion with collagenous degeneration and subsequent liquefaction, due to the large local dose of radiation at a high dose rate, has been reported by Lushbaugh et al., whose description of a plutonium lesion found in the dermis is very similar to that observed for plutonium in the lung.⁹'

"Richmond and co-workers continued these experiments with hamsters and the following appears in their latest progress report (Particular attention is drawn to the last sentence):

'Most of the animals placed on study early in the program have reached the end of their normal life span without developing significant pulmonary lesions. During the past few months, we have observed some histological changes in the lungs of very long-term animals (15-20 months). In these animals, an extension of bronchiolar epithelium into the alveolar ducts and alveoli has occurred. In some cases, the alveoli are lined with cuboidal or columnar epithelial cells (Fig. 1). This lesion has been observed almost entirely in the higher activity levels (levels 4-6) and in animals given relatively small numbers of spheres (2000-6000). An interesting recent observation has been given larger numbers of spheres of approximately 60,000. This group of animals has been exposed only about 6 months. A consistent observation of this lesion after drastically different induction times could lead to speculation that the amount of tissue irradiated is an important element in timing of the tumorigenic response. There has been no increase in frank tumors observed within the past year; however, the epithelial changes described above could be considered as precursors of peripheral adenomas.¹⁰'

9/ Richmond, C.R., et al., "Biological response to small discrete highly radioactive sources," Health Physics 18, 1970, p. 406.

10/ Richmond, C.R. and Sullivan, E.M., (eds.), Annual Report of the Biomedical and Environmental Research Program of the LASL Health Division for 1973, Los Alamos Scientific Laboratory Report LA-5633-PR, May 1974, p. 7.

"The particle activity in these hamster experiments was considerably lower than that associated with the excised palmar lesion and the lesions in the rat experiments. The particle activity from the excised palmar lesion was 5 nCi and those in the rats experiment were 40 nCi and greater. The level 4 particles in the hamster experiment contained only 4.3 pCi and level 6 contained 60 pCi. The initial lesions observed surrounding these lower activity particles were called granulomas measuring 200-500 μ in diameter (about the same size as the excised palmar lesion).¹¹

"It is of importance to compare the description of the lesion in the hamsters wherein there is an extension of the bronchiolar epithelium into the alveoli. This is a suggested mechanism for the histogenesis of bronchiolo-alveolar carcinomas.¹² Moreover, the description of the hamster lesions indicated that, in some cases, the alveoli are lined with cuboidal or columnar epithelial cells. Such lining cells are a histological feature of bronchiolo-alveolar carcinoma.¹³ We see no reason for being complacent about these lesions.

^{11/} Richmond, C.R. and Voelz, G.L., (eds.), Annual Report of the Biomedical and Environmental Research Program of the LASL Health Division for 1971, Los Alamos Scientific Laboratory Report, LA-4923-PR, April 1972, p. 31.

^{12/} Evans, Winston R., Histological Appearance of Tumors, Second Edition, Williams and Wilkins Company, Baltimore, Maryland, 1966, pp. 1112-1113.

^{13/} Ibid., p. 1111."

This material was available to the NAS-NRC Committee at the time of our meeting with them and it was discussed at the meeting. Page 10 of the transcript of the meeting contains the following:

"DR. TAMPLIN: I think the impressive thing, or the thing that causes us to more or less stick tenaciously to this hypothesis are the lesions that have been produced around these particles in palmar tissue and in rat and in hamster lungs.

"The pathological description of the lesions suggests that you would not want to have too many of these lesions in human lungs.

". . . . It just seems to me that the description of those lesions should cause you to want to limit the number of hot particles in the human lung to a very few particles."

The authors of the NAS Report chose not to present the description of these lesions or even discuss the lesions, for that matter. It appears, however, that they did elect to discuss them obliquely in absentia. We refer here to the ending paragraph on page 11 of the body of the report and to pages A.72 and A.73 of Appendix A wherein precancerous lesions are briefly discussed. Clearly these remarks in the NAS Report would appear irrelevant to the uninitiated since the underlying basis for them, the lesions, are not mentioned. The following appears, unheralded, on page 11 of the body of the NAS Report:

"Within the present insufficient body of knowledge about carcinogenic processes and tumor biology, the concept of 'precancerous lesions' has developed. Precancerous lesions are those which may precede and may favor the development of cancer but do not possess the essential elements of the disease.⁶⁶ However, although most so-called precancerous lesions have some neoplastic properties, such as cell proliferation and distortion, it is impossible to predict whether they will in fact develop into cancer. Tumor induction is the result of a series of critical events which are still imperfectly understood. The terms precancerous, pre-adenoma, etc. are used to indicate changes reminiscent of those preceding or concomitant with tumor development, but they do not have precise scientific meanings."

Since the particle produced lesions were not discussed in the NAS Report, it is not clear what the NAS Committee meant to

imply by the above quoted paragraph. Science is not always precisely quantitative and this is particularly true in many cases where science must be applied to the practice of public health. The NAS Committee should have discussed these lesions and should have discussed (albeit, not in precise quantitative terms) the risk associated with the lesions. We do not argue that any one particular lesion will develop into a cancer; rather, we suggested that the chance of any one lesion becoming a cancer is 1 in 2000. Concerning this probability estimate, we stated on page 9 of our Supplemental Submission to the EPA:

"In our Hot Particle Report we assumed a cancer risk of 1/2,000 per particle produced lesion. This value was derived from the tumor risk per atrophied hair follicle in the experiments of Albert, *et al.* (see page 4). To our knowledge this is the only biological data that quantitatively relates the radiation induced disruption of a tissue mass to cancer production. As we indicated in our Hot Particle Report, this risk estimate is not necessarily conservative. One could argue that the descriptions of the particle produced lesions cited above suggest a greater risk. We can see no justification for assignment of a lower risk. While we have been criticized for using rat skin data to estimate the risk in human lungs, we have not seen any suggestion for a better approach that is based upon available biological data."

The use of the terms precancerous and preadenomatous in the literature is not capricious. Lesions so described are not risk free. Hot particles produce such lesions. Given the description of the lesions observed in human palmar tissue and in rat and hamster lungs, it is not necessary to invoke the rat skin data to argue that the number of such lesions in

human lungs should be limited to a very few. The NAS Committee should have indicated what they thought was acceptable -- a few, 10 or 100 or more. As it stands, the NAS Report leaves the impression that these lesions are insignificant and that is clearly not correct.

THE COCHRAN-TAMPLIN RATIONALE

Pages 5-8 of the NAS Report contain the committee's discussion of the rationale for our hot particle hypothesis. This discussion bears a curious resemblance to a paper prepared by the committee chairman, Dr. Roy E. Albert, on March 24, 1974. This report predates the formation of the NAS Committee and was submitted as part of the AEC testimony at the EPA Hearings on Plutonium and Other Transuranics.

Since this paper of Albert misrepresented the rationale for our hypothesis, we find it incomprehensible that its essence should be included in the NAS Report. This is particularly confounding since we had met with the committee to clarify any misunderstanding. Moreover, at the time of that meeting, our Supplemental Submission to the EPA hearings had been available to the committee for some months. The meeting, thus, should have served to clarify issues left unresolved by our Supplemental Submission to the EPA hearings. We thought it did, and the record of the meeting seems to confirm this.

Pages 5 and 6 of the NAS Report contain mainly quotations from our initial Hot Particle Report. Page 6 contains a brief

discussion of our Supplemental Submission to the EPA hearings. This brief discussion fails to mention that the Supplemental Submission stressed the significant support for our hot particle hypothesis that is obtained by the hot particle produced lesions as discussed above. Moreover, it fails to explain that, based upon new data related to particle size distributions and the particle produced lesions, we were able in the Supplemental Submission to the EPA hearings, to arrive at a better definition (an operational definition) of the minimum activity to constitute a hot particle and that this allowed us to abandon the definition based upon the dose to the surrounding tissue. As a result, we suggested that a minimum activity of 0.6 pCi was more appropriate than the initial value 0.07 pCi that was based upon a dose of 1000 rem/year to the surrounding tissue.

It is thus grossly misleading to state, as on page 5 of the NAS Report, that our rationale is based "almost wholly on the rat skin experiments of Albert and his co-workers." As we stated near the close of the above discussion of the hot particle produced lesion, "Given the description of the lesions observed in human palmar tissue and in rat and hamster lungs, it is not necessary to invoke the rat skin data to argue that the number of such lesions in human lungs should be limited to a very few."

On page 2 of our Supplemental Submission to the EPA hearings, we stated our hot particle hypothesis:

"The 'hot particle hypothesis' is relatively simple. Qualitatively, the hypothesis is:

When a critical tissue mass is irradiated at a sufficiently high dose, the probability of tumor production is high.

A corollary to this is:

When a critical tissue mass in the lung is irradiated by an immobile particle of sufficient alpha activity the probability of a lesion developing approaches unity, and the probability of this lesion developing into a tumor is high.

Much of the discussion during our meeting with the NAS Committee had to do with clarifying this hypothesis. It would appear however that in preparing this section of the NAS Report (pp. 5-8) the committee chose to ignore our Supplemental Submission to the EPA hearings and our meeting with the committee and to, instead, rely heavily upon the material prepared by the committee chairman in March, 1974:

On page 6 of the NAS Report, the following appears:

"The Committee views the Cochran-Tamplin thesis as based on three assumptions. Assumptions 1 and 2 together form the Geesaman Hypothesis and Assumption 3 is the Hot Particle Hypothesis. The assumptions are described and commented on below."

We shall discuss each of these assumptions in turn but first we wish to point out that our hypothesis is not based upon 3 assumptions; rather it is based upon observational data and one assumption. The observational data are the particle produced lesion of suspect prognosis. The assumption, which relates to quantifying the hypothesis, is that the risk of any one of these suspect lesions developing into a tumor is 1/2000.

Page 6 contains the committee's first assumption:

"Assumption 1

The correlation between the induction of atrophic hair follicles and the induction of tumors in rat skin with ionizing radiation¹⁸⁻²¹ is assumed by Cochran and Tamplin to indicate that the atrophic hair follicle causes the skin tumors and that the role of ionizing radiation is only to produce the structural damage to the hair follicles."

We never made any such assumption. On page 8 of our Supplemental Submission to the EPA hearings, we stated:

"While we have here stressed the formation of the lesion surrounding the hot particle, it is important to recognize that many of the cells on the periphery of the lesion are the progeny of cells that received radiation damage during the formation of the lesion."

Moreover, on page 9 of our Supplemental Submission to the EPA hearings, we stated:

"In our Hot Particle Report we assumed a cancer risk of 1/2,000 per particle produced lesion. This value was derived from the tumor risk per atrophied hair follicle in the experiments of Albert, et al. (see page 4). To our knowledge this is the only biological data that quantitatively relates the radiation induced disruption of a tissue mass to cancer production."

Clearly, we had never intended to separate the radiation induced tissue disruption from the other radiation effects and we made this clear at our meeting with the NAS Committee. The following appears on pages 18-19 of the record of that meeting:

"DR. ALBERT: Then it would be incorrect actually to say that what you are driving at is that the architectural disruption itself is the cause of cancer?"

"DR. TAMPLIN: Probably we would suggest that it enhances the chance of cancer developing, given the fact that there is also radiation injury involved in the surrounding tissue."

Later on page 24 of the same record is found:

"DR. RADFORD: I would like to ask a question and then get a reaction in terms of observations that have been made in man.

"The question I would like to ask is, coming back to the point that Roy was stressing, namely you are postulating that it was the partial radiation damage or lower dose radiation damage, however you want to define it, at the periphery of the lesion, coupled with the tissue disorganization that went with it, which might constitute the major concern about this.

"Am I correct in inferring that you are accepting or at least have this kind of model in mind too as a possible explanation of the hot particle effect?

"DR. TAMPLIN: I would say that is the case. In other words, we have not fine tuned the model. The observations more or less speak for themselves, pathological descriptions of the lesions that were produced."

Considering the above and the more detailed discussion during our meeting with the NAS Committee, we are at a complete loss to understand why the committee chose to so blatantly misrepresent our rationale in the NAS Report. There is neither logic nor justice in the committee's rejection of our hypothesis by resorting to a discussion of their own fabrication.

On page 7 , the committee presents its second assumption:

"Assumption 2

Geesaman^{15,16} generalized (Assumption 1) that follicle atrophy causes skin tumors in the rat. He expanded this assumption to conclude (as Assumption 2) that the probability of cancer due to focal tissue damage in the lung caused by a microscopic plutonium particle

will be 1/2000, which is the hypothesized ratio of tumors-to-atrophic follicles in the rat skin."

The subsequent discussion of this assumption on page 7 of the NAS Report is related to the erroneous Assumption 1. Since we did not assume that the tissue damage, per se, was the sole cause of cancer, the discussion is not relevant. As discussed above, we indicated that the local tissue disruption coupled with other radiation effects leads to an enhanced cancer risk. In this respect, it is significant to note that the March, 1974 report prepared by the NAS Committee's chairman contained the following on pages 317-319:

"Although tissue damage cannot be assigned a primary causal role in cancer induction, there are various ways in which tissue damage could contribute to tumor formation. One possibility is that the killing of a portion of cells in the target tissue has the consequence of stimulating the survivors to proliferate in order to restore the cell population. There is evidence that neoplastic transformation does not become fixed unless cell division occurs within a relatively short period after carcinogen exposure. This is true for ionizing radiation (10) and viruses (11). The likelihood of producing transformed cells could thus be increased by provoking cell division particularly in a tissue which normally has a low rate of proliferation.

"There is evidence that neoplastically transformed cells in physical contact with normal non-transformed cells are inhibited from proliferating (12). Tissue injury could free transformed cells from this type of growth restraint.

"It is possible that an area of tissue, heavily damaged by a carcinogen, particularly with scar formation, would constitute an immunologically privileged site and thus interfere with important defense mechanism against neoplastically transformed cells (13).

"There are several other speculative ways in which damage could contribute to tumor formation which can be mentioned: cell damage might interfere with repair of carcinogen-induced DNA damage; dedifferentiation of surviving cells in a heavily damaged organ could make them more susceptible to infection by oncogenic viruses, as with the irradiated thymus (14); in the case of chronic carcinogen exposure the increased cell proliferation induced by tissue damage could make cells more susceptible to the transforming action of a carcinogen.

"Although all of the above mechanisms for the enhancement of carcinogen effects by various forms of tissue damage have some basis in scientific evidence, the degree of importance as contributing factors has not been established."

These important comments were omitted from the NAS Report; yet, they are quite supportive of our rationale for the hot particle hypothesis. For example, we stated on page 8 of our Supplemental Submission to the EPA hearings:

"It is reasonable to propose that these lesions disrupt the local tissue architecture and thereby interfere with the normal bio-chemical and physical communication between the cells that control processes such as contact inhibition which are responsible for maintaining tissue stability. They thus create an area with an increased cancer risk.

"While we have here stressed the formation of the lesion surrounding the hot particle, it is important to recognize that many of the cells on the periphery of the lesion are the progeny of cells that received radiation damage during the formation of the lesion."

The pathogenesis of the radiation induced neoplasia in the beagle dog experiments as described by Dagle, et al.,^{*/}

*/ G.E. Dagle, J.E. Lund and J.F. Park, "Pulmonary Lesions Induced by Inhaled Plutonium in Beagles," pp. 161-168. In: The Health Effects of Plutonium & Radium (W.S.S. Jee, ed.). The J.W. Press, Salt Lake City, UT, 1976.

is highly supportive of this proposed mechanism:

"Although the lesions of radiation injury due to plutonium have been described, the critical steps in the development of these lesions in dogs remain unknown. The most interesting feature in their development is the apparent progression of epithelial changes to neoplasia. At the dosage levels studied, the dogs either died from severe radiation pneumonitis or, at lower doses, less severe pneumonitis and pulmonary neoplasia."

* * *

"If the particles are sequestered, either intra- or extra-cellularly, continued local injury would result, with eventual repair by fibrosis. Epithelial cell proliferation could result from continued radiation-induced cell death, or more likely, secondary to the focal fibrosis and chronic inflammation. Epithelial cell metaplasia in association with focal interstitial fibrosis attributed to lungworm infection has been reported in beagle dogs (Hirth and Hottendorf 1973). Similar atypical or dysplastic epithelial cells have been observed secondary to fibrotic lesions resulting from a variety of known and unknown causes in man. In some cases, transition to carcinoma has been reported (Fraire and Greenberg, 1973). It is interesting and perhaps of significance that one-third of the lung carcinomas in man reported to be associated with fibrosis have been classified as bronchiolo-alveolar cell types, whereas this type accounts for only 3-6% of total lung tumors in man (Fraire and Greenberg 1973). This is the predominant tumor observed in the Pu-exposed dogs. The stimulus for epithelial cell proliferation and transformation in association with fibrosis is not known and, at present, the existence of such a stimulus is only speculative. The possibility that fibrosis may render the proliferating epithelial cells more susceptible to chemical or physical carcinogenesis cannot be excluded."

In summary, we did not resurrect an ancient theory that chronic injury was the sole cause of cancer. We discussed an injury mediated mechanism where the local tissue disruption was caused by radiation and where the disturbed tissue mass (lesion) contained viable cells that received radiation injury during the formation of the lesion.

The Committee's third assumption appears on page 7 of the NAS Report:

"Assumption 3

"On the basis of Assumption 2, Tamplin extends the Geesaman Hypothesis to make Assumption 3: when the dose to the surrounding tissue from the alpha-emitting particle exceeds 1000 rads/yr, focal damage will be produced with a cancer risk of 1/2000. This is the Hot Particle Hypothesis."

This is really a quantification of the Hot Particle Hypothesis as presented in our original report prepared in support of our petition. The 1000 rads/year (should be 1000 rem/year) value was our approach to estimating the minimum activity to constitute a hot particle. This was based upon the dose to the surrounding tissue. However, as we indicated at the beginning of this section, new information related to hot particle produced lesions and particle size distributions became available subsequent to the submission of our petition. This new information allowed a better definition (an operational definition) of a hot particle. This new approach was presented in our Supplemental Submission to the EPA hearings where we suggested that the minimum activity to constitute a hot particle was, more appropriately, 0.6 pCi rather than the value of 0.07 based upon the 1000 rem/year dose to the surrounding tissue.

We certainly did not expect the analysis of hot particle related data to end with the submission of our petition and clearly, that is why we modified our definition of a hot particle by analysis of newly developed data. The important

factor is not our initial attempts to quantify the hypothesis but that hot particles do produce lesions of suspect prognosis and the important issues are (1) what constitutes a hot particle and (2) what is an acceptable limit for hot particles in the human lung.

We have on pages 7-8 of this critique discussed our risk estimate of 1/2000. Relative to that discussion, we shall reiterate that the description of the particle produced lesion is, in our opinion, sufficient to suggest that the number of such lesions in the human lung should be limited to a very few. If the NAS Committee is of a different opinion, they should state what is acceptable; a few, 10 or 100 or more.

Page 8 of the NAS Report presents a "Summary Evaluation of the Cochran-Tamplin Rationale." The last sentence on page 8 reads, "Therefore, the rationale for the NRDC petition appears indefensible." Since, as we have shown above, the NAS Committee did not discuss our rationale but, rather, discussed their own fabrication, this conclusion by the committee is completely without merit.

THE BEAGLE DOG DATA

Pages 13-15 of the NAS Report discuss an analysis of the beagle dog data. On page 1, the NAS Committee appears to indicate that this analysis is a keystone in its argument against the hot particle hypothesis. This analysis is presented in detail on pages A.54 to A.62 of Appendix A of the NAS

Report. The analysis was prepared by Dr. E.B. Lewis.

In this analysis, Lewis made an estimate of the rate at which "lethal lung tumors" developed in 39 beagle dogs that had been exposed to plutonium and followed for the duration of their life. To do this, he used the life-table method and computed the "lung tumor mortality rate" for each 100 and 400 day period following exposure. This mortality rate is then set equal to $(1-e^{-m})$, where m represents the mean number of "lethal tumors" per animal which are assumed to be Poisson distributed. Lewis defines a "lethal tumor" as "One which has developed to the point at which it is capable of causing the animal's death." Since his values of m are derived from mortality data and not from the actual count of the numbers of tumors per animal, m is no more than a mathematical construct. Moreover, the evidence indicates that the mathematical construct, m , is even further removed from any real correlation with the actual biological processes of tumor induction and growth. The Lewis construct would treat the tumors in these animals as primary or solitary growths. The evidence, however, demonstrates that the tumors were not primary or solitary tumors but, rather, were tumor masses that represented the overgrowth of numerous primary tumor sites. A description of the histopathology of the dogs that died 24-48 months post-exposure was given by Parks, et al., in 1964:

". . . The principal changes observed in the lungs of the dogs that died spontaneously consisted of thickening of the pleura with extension of the

fibrosis into the parenchyma, and severe subpleural, septal, and peribronchiolar fibrosis (Figs. 12, 13). Attendant with this scarring were numerous foci of alveolar cell, bronchiolar, and squamous metaplasia (Fig. 14). In addition to the above changes, four of the dogs (215, 83, 173 and 106) had bronchiolo-alveolar tumors. All of the tumors were peripheral or subpleural in location. All were multicentric in origin, except in Dog 173 where only one neoplasm in the right apical lobe was observed. The neoplasms were associated with scarring and numerous foci of alveolar metaplasia, some of which showed transition to anaplastic and neoplastic cell forms (Figs. 15, 16)."/>* / [Emphasis supplied.]

In a 1972 report on the progress of these experiments, the lung tumors were described as:

"The majority of the tumors were peripheral in primary site of origin, usually appeared to be multicentric, and were rather slow to invade the lymphatics or vascular system."** / [Emphasis supplied.]

Clearly, the mathematically constructed m values are not a measure of the number of primary tumor sites in these dogs. Nevertheless, on page 14 of the NAS Report, this calculated m value is used purportedly to demonstrate that we have over-estimated the hot particle effect by a factor of 50 when the minimum activity to constitute a hot particle is 0.6pCi. The factor of 50 was obtained by comparing Lewis' m value at 3600 days post-inhalation (m=1.9 tumors per dog) with the NAS Committee's estimate of what the hot particle hypothesis would predict (100 tumors per dog). Besides the fact that the m value is no more than a mathematical construct, there are other reasons why this comparison is meaningless and why it should not have been undertaken.

* / J.F. Park, W.J. Clark, and W.J. Bair, Chronic Effects of Inhaled Plutonium in Dogs, Health Physics 10, p. 1216, 1964.

** / J.F. Park, W.J. Bair, and R.H. Busch, Progress in Beagle Dog Studies with Transuranium Elements at Battelle-Northwest, Health Physics 22, p. 805, (June, 1972).

First, it is not clear to what extent the tumor incidence in these dogs is related to the hot particle effect. It must be recognized that the entire lungs of the dogs were exposed to substantial alpha doses. As indicated by Dr. Bair on page A.46 of Appendix A, "All dogs with pulmonary neoplasia also showed extensive fibrosis." Thus, it is not clear whether this overall radiation exposure of the lungs masked or contributed to the hot particle effect.

In fact, as Lewis showed on pages 14 and A.60-A.62, the overall radiation exposure of the lung was such (26,000 rem) that on the basis of the risk estimate from the BEIR Report all the dogs would have been expected to develop lung cancer. Clearly, the exposure in the beagle dogs was so high that it is not possible to draw inferences with respect to exposures at lower doses whether one is dealing with the hot particle hypothesis or with uniform radiation.

Second, if any comparison was to be made, it should not have been made with the mathematical construct of Lewis but with the actual number of primary tumor sites. In a recent telephone conversation, we questioned Dr. Park about the multicentric nature of the tumors. He informed us that the examination of the lungs consisted of a gross examination for visible or palpable tumors and a subsequent histological

examination of representative slides of each lobe. The latter consisted of about a half dozen slides (approximately 2cm X 3cm X 5 μ). The histological examination, thus, involved less than 1% of the lung tissue. Yet, Dr. Park informed us that this histological examination in the animals that died with tumors yielded up to 10-20 microscopic tumor sites. This indicates that an examination of less than 1% of the lung tissue yielded, on the average, a few tumor sites per dog. This would suggest an average yield of more than 200 tumor sites per dog or a factor of more than 100 -fold greater than the value of 1.9 obtained by the mathematical construct of Lewis.

The latter value, 200 tumor sites per dog, corresponds to what might have been estimated by the hot particle hypothesis. However, it cannot be determined how many of these are primary sites and how many are metastases. Moreover, as stated above it is not clear whether this tumor incidence is a response to hot particles or to the overall exposure of the lung to alpha radiation.

* * * * *

In summary, we feel that the results of the beagle experiment are so equivocal that this analysis in the NAS Report is meaningless.

Page-by-Page Critique

In the above sections of this report we discussed what we considered to be the major flaws in the NAS Report. In this section we shall critique the remainder of the report. The headings here will refer to the page numbers in the NAS Report and its Appendix A.

Page iii

On this page, the committee makes special note of their meeting with Drs. Cochran and Tamplin. It is unfortunate, as we indicated in the main portion of this critique that the committee ignored the substance of our comments at that meeting.

Page 1

This page presents the committee's summary and conclusions. As we indicated in the main body of this critique, the conclusion that the evidence does not support the hot particle hypothesis is unwarranted. While the committee summarizes their concept of the current state of knowledge about the "hot particle" problem, it is significant to note here that the committee fails to mention that hot particles have been observed to produce lesions of suspect prognosis -- suspect because the lesions are suggestive of an incipient carcinogenic response. This we propose is one of the major bits of knowledge relative to "hot particles."

In this summary, the committee raises three points. The first relates to their analysis of the beagle dog experiments. In the previous section of this critique, we have shown this analysis to be incorrect on several grounds.

The second point suggests that since the tracheobronchial region is more sensitive to radiation in man, the application of risk factors obtained from the uniform irradiation of this region are adequate for estimating the risk to the alveolar regions. We agree with this so far as uniform irradiation is concerned, but hot particles result in a highly non-uniform tissue irradiation and, as the hot particle produced lesions suggest, a different carcinogenic mechanism. As we stated in our Supplemental Submission to the EPA hearings on page 21:

"In his statements and questions during the December 10 and 11, 1974, hearings, Dr. Radford implied (and attempted to solicit concurrence) that hot particles can only be expected to induce cancer in man in the more proximal bronchi because in man this is the sensitive tissue. We cannot agree with this and as the transcript (pages 2-262 to 2-268) indicates, Dr. Bair did not concur.

"While the predominant lung tumor in man is bronchiogenic, bronchiolo-alveolar carcinomas also occur. It would appear that because of genetic factors, influenced by the prevalent carcinogens, the more proximal bronchi are the most sensitive tissue. Nevertheless, we submit that alpha-emitting hot particles represent a new and unique carcinogenic agent. As such, we see no a priori reason for doubting that, as in animals, bronchiolo-alveolar carcinoma will be induced in man by PuO₂ deposited in the peripheral regions of the lungs."

This conclusion appears to be shared by Bair, who with Thomas^{*/} recently noted:

"Bronchiolo-alveolar carcinoma, the predominant lung tumor type observed in animals exposed to plutonium, is relatively uncommon in human beings, accounting for only 3 to 6 percent of total lung cancers. However, if plutonium irradiates the same regions in both human and experimental animal lungs, there is every reason to expect that the resulting tumors would be of similar cellular origin."

*/ W.J. Bair and J.M. Thomas, Prediction of the Health Effects of Inhaled Transuranium Elements from Experimental Animal Data, IAEA-SM-199/58.

One final point in this regard, Dagle et al. ^{*/} (quoted on pp. 14-15 of this critique) noted,

"It is interesting and perhaps of significance that one-third of the lung carcinomas in man reported to be associated with fibrosis have been classified as bronchiolo-alveolar cell types, whereas this type accounts for only 3-6% of total lung tumors in man (Fraire and Greenberg 1973). This is the predominant tumor observed in the Pu-exposed dogs."

The committee's third point is that current evidence indicates hot particles do not represent a greater hazard than the same radioactivity distributed uniformly. The experimental evidence presented in the NAS Report is essentially the same material presented in WASH-1320. The same is true of the theoretical discussions in the NAS Report. In our critique of WASH-1320 we demonstrated that the experimental evidence was either irrelevant to the hot particle hypothesis or supportive of it. So far as the theoretical discussions were concerned, we indicated that they were relevant to a different mechanism of carcinogenesis. The same applies to the evidence and discussions in this NAS Report. Again, it is important to note that the most supportive evidence relative to the hot particle hypothesis, the particle produced lesions, are only discussed obliquely and in absentia in this NAS Report.

*/ G.E. Dagle, J.E. Lund and J.F. Park, "Pulmonary Lesions Induced by Inhaled Plutonium in Beagles," pp. 161-168. In: The Health Effects of Plutonium & Radium (W.S.S. Jee, ed., The J.W. Press, Salt Lake City, UT, 1976.

Page 2

We find no objection to this page which presents the definition of the problem except for the last sentence which suggests that the committee used a far broader data base than we used to develop the rationale for our hypothesis. We submit that we reviewed the majority of the data and literature cited by the committee. However, in the presentation of the hypothesis, we did not cite irrelevant literature. In our critique of WASH-1320, we did discuss this extraneous literature. We had hoped that this NAS Report would not discuss this extraneous literature without recognizing our arguments concerning its irrelevance. We had hoped that this NAS Report would put an end to this intersection of monologues on this important subject. It appears, however, that that hope was in vain.

Pages 3-4

We have no objection to these pages that discuss the historical background except that we feel that the committee should not have placed the rather superficial reports of the BMRC, NCRP, and the NRPB on the same level as the rather comprehensive WASH-1320 prepared by Bair, Richmond and Wachholz. At the same time, we wish to reiterate our concern that the committee did not address our criticism of WASH-1320.

Pages 5-8

These pages present the committee's impression of the Cochran-Tamplin rationale. We have discussed this section in an earlier section of this critique. As we indicated there, the committee did not discuss our rationale but, rather, their own fabrication.

Pages 9-15

These pages are said to represent the current status of the radiation biology of inhaled alpha-emitters. Considering that the world is contemplating embarking on an era where plutonium will represent the primary fuel, we find little solace in this section of the NAS Report. A footnote here indicates that detailed supporting discussions are included in Appendix A. We shall critique these subsequently.

Pages 9-10

We have no criticism of these pages except for the section, inappropriately entitled the physics of energy absorption, that begins with the observation that the traversal of a cell nucleus by a single alpha particle is capable of killing or sterilizing the cell. From this they conclude that a hot particle would kill all the cells within the range of its alpha particles and thus be less tumorigenic than more uniformly distributed plutonium on much smaller particles. Since the committee chose not to discuss the hot particle produced lesions, they also failed to reconcile this theoretical conclusion with the lesions. The precise mechanism for the development of these lesions is unknown, but the evidence indicates that the lesions develop with a dynamic

and that cells on the periphery are the progeny of cells that underwent radiation damage during the formation of the lesion. Moreover, as we have pointed out, plutonium separated from reactor fuel will be contaminated with beta-emitting isotopes that could continually subject the cells on the periphery to beta radiation. As a result, reactor fuel plutonium could be more hazardous than weapons grade plutonium.

Ultimately, we propose that the lesions speak for themselves and suggest that the disruption of a small tissue volume by radiation represents a unique carcinogenic event. Hot particles, we propose, represent a new and unique carcinogen that lies outside existing theories of radiation carcinogenesis.

Page 10

This page discusses the observation that more chromosome aberrations are found after uniform irradiation than after particulate irradiation. It is then stated that insofar as these aberrations are related to cancer risk, uniform radiation is more hazardous. Since the relationship between the aberrations and cancer is not known, the conclusion is speculative as the committee stated. The mechanism(s) of radiation carcinogenesis are unknown and, consequently, we again state that the particle produced lesions speak for themselves.

This page also discusses mechanisms of carcinogenesis. The discussion here appears to be an oblique response to the particle produced lesions and we have discussed this in above sections of this critique. Words such as precancerous are not used in a capricious manner in the scientific literature.

Pages 12-15

These pages discuss animal experiments. Pages 13-15 discuss the beagle dog experiments that we discussed in the previous section of this critique where we demonstrated that the committee's analysis of this experiment is erroneous. Page 12 briefly mentions various experiments on rats and hamsters. We shall critique these experiments as we move to Appendix A of the NAS Report where they are described in more detail. It is worthwhile to point out here, however, that no mention of the particle produced lesions in the rats and hamsters is made either here or in Appendix A.

On page 13, the committee states that these animal experiments indicate that the carcinogenic response to alpha irradiation of the lung is largely independent of its distribution. In our subsequent discussion of these experiments, we demonstrate that this conclusion is unwarranted particularly with respect to hot particles.

Page 15

This page discusses experience with human beings. Here it is stated that, since the most prevalent lung cancer in man is bronchiogenic, man may be less sensitive to plutonium because it has been shown to produce mainly bronchiolo-alveolar carcinoma in animals. We have discussed this above relative to page 1 of the NAS Report where we pointed out that hot particles represent a new and unique carcinogen and, therefore, there is no a priori reason to state that they will not produce bronchiolo-alveolar carcinoma in man. It must be recognized that such cancers do appear in man.

Pages A.1 to A.77

These pages, as stated in the main body of the NAS Report contain the detailed information upon which the committee's conclusions were based. Our critique of the main body of the NAS Report demonstrates we cannot agree that this appendix supports the committee's conclusions. Many of the statements in the main body of the NAS Report present the aura of being unequivocal, yet much of the material and analyses in Appendix A are presented in a superficial manner. Moreover, the various presentations are not consistent and this should have resulted in equivocal statements in the main body of the report and as a consequence the committee could not have rejected the hot particle.

As a prime example of this inconsistency and lack of equivocation, we offer the model presented by Dr. Gregg on pages A.23 to A.30. The essence of this presentation is discussed in an unequivocal manner on page 11 of the main body of the report. For one thing, the committee fails to mention that this is only one model or hypothesis and that it cannot be used to set aside another hypothesis such as the hot particle hypothesis. In addition, on page A.66, Dr. Goldman states:

" . . . despite intensive study, the exact mechanisms of radiation-induced cancer are still unknown. Many theories have been proposed, usually invoking a series of initiating and promoting factors for which some data is available, but it appears that no single model is universally acceptable. 89/"

Reference 89 refers to a paper by G.W. Casarett, also on the NAS Committee, who authored the section of the report, Mechanisms of Carcinogenesis. Casarett begins this section (p. A.72) by stating:

"The cellular processes that cause neoplastic transformations are unknown."

Dr. Bair, another member of the committee, was the principal author of WASH-1320. In WASH-1320, a model proposed by Dean and Langham in 1969 was reviewed together with several others and the authors of WASH-1320 concluded:

"These dosimetric models can be useful in understanding how a given biological effect such as cancer occurs following deposition of plutonium in lung and might even lead to identification of possible mechanisms for cancer induction.

"However, because these models are deficient with respect to the biological aspects of plutonium in lung (in most cases for the simple reason that the biology is not adequately known), the models are not dependable for predicting the health consequences of plutonium. In fact these models can be used to yield almost any answer desired."

Clearly, reference to this model of Gregg in the main body of the NAS Report should have been equivocal. We shall discuss this further with reference to the appropriate sections of Appendix A.

Pages A.1 to A.6

We generally agree with this discussion of physical and chemical characteristics of alpha-emitting aerosol particles associated with nuclear fuel.

Pages A.7 to A.18

We generally agree with this discussion of the respiratory tract structure and function.

Pages A.19 to A.23

We generally agree with this review of the models and experimental data related to clearance (and retention) of inhaled particles from the lung.

Pages A.23 to A.24

We generally agree with this discussion of basic particle dosimetry.

Pages A.24 to A.30

These pages present a primitive model(s?) of the mechanism of radiation carcinogenesis from alpha particles developed by Dr. Gregg. Regardless of its sophistication, this is only one of many models or hypotheses and, as such, is not capable of setting aside the hot particle hypothesis. Moreover, there is no attempt in this report to reconcile the model with any of the experimental data presented in the report or with alternate models or hypotheses.

Dean and Langham, for example, developed a model that was also based upon assumptions relative to the rat skin experiments. Their model came to a completely opposite conclusion concerning the hazard of particulate radiation. It indicated that the hazard would increase with particle size and reach a maximum at 1μ diameter for Pu-238 and at 8μ diameter for Pu-239. It estimated a risk per Pu-239 particle of 1×10^{-4} at a particle diameter of $\sim 0.8\mu$ and a risk of 10^{-1} at a diameter of $\sim 8\mu$. On page A.26, Dr. Gregg indicates, on the other hand, that there is no apparent reason (based on his model) to support the concept of increased risk per particle above an activity of 0.005 pCi of Pu-239 (diameter $\sim 0.25\mu$). The maximum risk per particle predicted by Gregg's model is $\sim 1 \times 10^{-6}$ (page A.27).

Gregg's model is especially primitive with respect to the cells at risk in the lung. He estimates a range for the alpha particles of 182μ and a total of 1,240 affected cells. With a more descriptive model of the lung, Geesaman estimates a range of 1000μ for some alpha particles and a total of some 100,000 affected cells. Geesaman's estimate corresponds to the model being developed at Los Alamos using photomicrographs and the Monte Carlo computation technique. These more sophisticated models indicate, contrary to Gregg's model, that a large number of cells on the periphery of particle produced lesions underwent alpha irradiation during the formation of the lesion. Applying Geesaman's estimate of the number of affected cells to Gregg's calculation on page A.27 leads to a risk per particle of $\sim 1 \times 10^{-4}$ which is close to our suggested value of 5×10^{-4} . We do not mean to imply a great deal of significance to the comparison. Rather, we use it to fortify the statement in WASH-1320:

"These dosimetric models can be useful in understanding how a given biological effect such as cancer occurs following deposition of plutonium in lung and might even lead to identification of possible mechanisms for cancer induction. However, because these models are deficient with respect to the biological aspects of plutonium in lung (in most cases for the simple reason that the biology is not adequately known), the models are not dependable for predicting the health consequences of plutonium. In fact these models can be used to yield almost any answer desired."

Clearly, this model of Gregg cannot be used as any substantial refutation of the hot particle hypothesis and such a disclaimer should be included in its presentation in the NAS final report.

Pages A.30 to A.36

The material presented here, primarily a review of studies of cell survival following irradiation of cells in vitro, is relevant to some models of cancer risk based principally on the killing of cells, for example, the model proposed by Gregg discussed above. The material, however, is not useful in testing the hot particle hypothesis which is based on a radiation-induced injury mediated mechanism of carcinogenesis with an intermediate state being lesions of the type observed in the human palmar skin, hamster and rat lung.

The bottom line or conclusion of this section (p. A.36) is:

"Insofar as cell killing may be related to cancer risk, the in vitro data would suggest that the radiation effect is greatest when the alpha flux is diffusely distributed."

The "may be" in this sentence indicates the speculative nature of this section of Appendix A and as such it is consistent with the statement by Casarrett on page A.72:

"The cellular processes that cause neoplastic transformations are unknown."

Pages A.36 to A.53

These pages present a summary of animal experiments wherein the animals' lungs were exposed to alpha-emitting, transuranic elements. The animals involved were beagle dogs, rats and hamsters. We have discussed the beagle dog experiment elsewhere in this critique and will not repeat that discussion here. The exposure of the rat and hamster lungs in the studies summarized was to both soluble (non-particulate) and to insoluble (particulate) alpha-emitters.

The conclusions drawn on page A.52 are based upon an analysis of tumor induction on a per rad or per microcurie to tumor relationship. As we have pointed out in our critique of WASH-1320, such an analysis is not an appropriate test of the hot particle hypothesis. A test of the hot particle hypothesis must be made on a per particle basis.

Again, in this section of the NAS Report, the particle produced lesions in the rat and hamster lungs are not discussed. Moreover, this section does not

present the latest data available on the hamster study conducted at LASL.

We propose that when all of the evidence is considered and analyzed, the animal experiments can not be used to reject the hot particle hypothesis. These experiments, in fact, must be considered to support the hypothesis.

Pages A.36 to A.39

These pages present a summary of the dose-effect relationship in the animal experiments. As we have indicated above, dose is not the appropriate parameter to test the hot particle hypothesis.

Pages A.39 to A.42

These pages present the result of experiments wherein rat lungs were exposed to soluble compounds of Pu-239. In the two studies discussed here, the dose effect relationship below 3000 rem (300 rad) differs by an order of magnitude (3% to 30% tumor induction). This difference occurred even though Wistar rats were used in both experiments and the Pu was administered as the nitrate. The author offers an explanation for this difference on page A.42 proposing that the higher response resulted because the exposure was more uniform in the high response group. However, he comes to a completely opposite conclusion on page A.52 where he states that, if anything, non-uniform (particulate) irradiation is more effective on a per rad basis. (See also page 13 in the main body of the NAS Report).

We propose that the significances of these experiments is to demonstrate the variability in the dose effect relationship and that they suggest that rats are particularly sensitive to alpha irradiation of the lung. This latter suggestion is confirmed by other experiments discussed in this section of the NAS Report Appendix.

Pages A.42 to A.44

These pages discuss an experiment that primarily relates to the inhalation of $^{239}\text{PuO}_2$ aerosols by Sprague-Dwaley rats. In this case, a high tumor response was observed in the dose range below 3000 rem (300 rad). The exposure levels in this experiment were quite high (above 1600 rem) and, therefore, it is impossible to determine whether the response was due to radiation level delivered to the entire lung or due to the localized radiation from hot particles. Other experimental data presented on subsequent pages of this section demonstrate that rats are particularly sensitive to alpha irradiation of the lung at appreciably lower dosage levels. Hence, responses at these higher levels are of no value relative to the hot particle hypothesis.

These experiments discussed on these pages also deal with exposures of rats to soluble and insoluble Am-241. The results and exposure levels are comparable to those in the experiments discussed on the previous pages and are, therefore, of little value relative to the hot particle hypothesis.

Page A.44

These pages discuss the exposure of rats to soluble Pu-238. The results of this experiment at 300 rem (30 rad) are similar to those discussed above. Moreover, similar to the data presented in the tables on pages A.41, A.42 and A.43, this experiment indicates an appreciable tumor response is elicited in rats at a dosage of 90 rem (9 rad).

A continuation of these experiments is discussed on pages A.50 and A.51. In these later experiments the rats were exposed to insoluble and particulate PuO_2 and similar results were obtained. In this case, however, a significant tumor response was suggested at dosages in the range of 30 rem (3 rad). As we indicated in our Supplemental Submission to the EPA hearings, these results at low concentrations of PuO_2 and could be explained on the basis of the hot particle hypothesis.

We propose that these rat experiments are of no value in testing the hot particle hypothesis for two reasons. First, since the rat is so sensitive to uniform irradiation, it is impossible to isolate the effects of hot particles within the dosage range of the reported experiments. Second, it is reasonable to propose that the life span of rats is short relative to the induction period for the hot particle mechanism. We shall discuss this further in relation to the hamster experiments.

Pages A.44 to A.45

These pages discuss two other experiments that add little to the conclusions above.

Page A.46

This page summarizes the beagle dog experiment which we have discussed elsewhere and shown it to be incapable of resolving the hot particle issue.

The study discussed here involving PuO_2 and asbestos adds little to the conclusions concerning the rat data that were presented above.

Pages A.46 to A.48

These pages summarize the results of experiments in which hamsters were exposed to Po-210 by intratracheal injection. These experiments demonstrate that at doses above 150 rem (15 rad) hamsters are as sensitive to uniform alpha irradiation of the lung as are rats. The experiments are of no relevance to the hot particle hypothesis.

Pages A.48 to A.50

These pages discuss the experiments wherein hamsters were exposed to Pu bearing microspheres by intravenous injection. These spheres subsequently lodged in the capillaries of the lungs of the injected animals. The discussion of these pages of NAS Report Appendix is, however, incomplete in that it does not discuss the particle produced lesions that were observed in these experiments. These lesions as the experimentors state, "are considered by many to be neoplastic precursors."^{*/} (See also our discussion of pages A.72 and A.73). Moreover, all of the latest data on these experiments is not presented on page A.49. This latest data records more than the four tumors indicated on page A.49 and, in addition presents data on the frequency the particle produced lesions (these have been designated bronchiolar adematoid lesions and abbreviated, BAL).

This later data is the result of microscopic examination of tissue sections and, hence, it records microscopic tumors that were not previously observed. The latest data we were able to obtain on the tumor and BAL incidence is presented in Table 1.

*/ Smith, D. M., et al., Biological Effects of Focal Alpha Radiation on the Hamster Lung, in Biological and Environmental Effects of Low-Level Radiation, Vol. II, IAEA, IAEA-SM-202/410, 1976, p.124.

In examining Table 1, it must be recognized that the microscopic examination involved on the order of 1% or less of the lung tissue. Consequently, if the entire lung were examined, both the BAL and tumor incidence would be expected to increase significantly. There is little reason to doubt that at least 1 BAL per lung would be found if the entire lung were examined and more tumors would also have been found.

Table 1

# animal	Spheres/animal	Pci Spheres	BAL(%)	Tumors (%)
71	2000	0.22	1(1%)	--
71	2000	0.42	2(3%)	1(1%)
71	2000	4.3	2(3%)	--
71	2000	2.1	?	1(1%)
70	2000	13.0	--	--
72	2000	60.0	--	--
154	6000	4.3	9(6%)	2(2%)
148	6000	59.0	3(2%)	2(2%)
47	10,000	0.22	1(2%)	--
163	70,000	2.0	85(52%)	17(10%)
37	400,000	0.42	?	1(3%)
20	1,000,000	0.07	?	1(5%)

Moreover, it must be recognized that the data in Table 1 are not corrected for age at death. As we have pointed out previously, the average tumor induction period for the hot particle hypothesis may exceed the life span of the hamster. Had these experiments been performed in a longer lived animal such as the beagle dog, it is reasonable to assume that the BAL and tumor incidence would have been significantly higher. This supported by the experimental observations.

In the animals exposed to 2000 - 6000 microspheres, the lesions were observed only in the long term animals (15-20) months. However, in the animals given 60,000 spheres, the lesions were observed beginning at 6 months. This would indicate that the number of particle produced lesions increased with time until it reached a frequency where it could be detected by examining only 1% of the lung tissue. With the higher number of spheres, the induction rate (lesions/animal) was higher and the incidence reached the detectable level sooner. The same applies to the tumor incidence since it is correlated with but lags behind the BAL incidence.

The results of these experiments are not inconsistent with the hot particle hypothesis. The data strongly suggest that in a similar experiment with beagle dogs, a high incidence of lung tumors would occur. This conclusion is not contradicted by the observation that a significant tumor incidence is induced in hamsters by uniform alpha irradiation of the lung. Two different carcinogenic mechanisms are involved and in the case of hot particles, the induction period is compromised by the life span of the hamsters but that for uniform irradiation isn't.

In summary, the only animal experiments discussed in this section of the NAS Report Appendix that bears on the hot particle hypothesis are the hamster microsphere studies and these support the hypothesis.

Pages A.54 to A.62

These pages present the analysis by Lewis of the beagle dog experiment. We have commented on this in the body of this critique where we demonstrated that the analysis was flawed.

Pages A.63 to A.66

These pages discuss lung cancer in humans. It is here that the basis for the statements in the main body of the NAS Report on page 1 and page 15 is found. These statements suggest that the tissue at risk in man is the bronchial epithelium. We have responded to these statements earlier when they appear in the main body of the report.

Pages A.66 to A.71

We do not see the relevance of this discussion to the hot particle problem. It does not appear to have been utilized in the main body of the NAS Report.

Pages A.72 to A.73

These pages discuss mechanisms of carcinogenesis. We have commented on this in the main body of this critique relative to the discussion of precancerous lesions on pages 34-35 of the main body of the NAS Report.

With regard to the discussion of precancerous lesions, we refer the Committee to a chapter on precancerous lesions by L. G. Koss,^{**/} wherein he defines these as follows:

Precancerous epithelial lesions are morphologic abnormalities with microscopic characteristics of cancer confined to the epithelium of origin, i.e., showing no evidence of invasive growth. Such lesions are obligate antecedents of invasive carcinoma, i.e., invasive carcinoma always originates from a precancerous lesion. Such lesions, if not treated or otherwise molested, will progress to invasive cancer within a time span and in a proportion of

**/ Leopold G. Koss, *Precancerous Lesions*, Chapter 5 from *Persons at High Risk of Cancer*, edited by Joseph Fraumeni, Jr., (Academic Press, New York) 1975, pp.85-102.

cases that may vary from organ to organ. The rate of invasive cancer following these lesions must exceed, in a statistically significant fashion, the rate expected in a normal population. Alternately, if such lesions are removed or destroyed, cancer will not develop from this particular site or organ. There is no conclusive information as to whether such lesions can regress spontaneously.